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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,159	07/24/2003	Vinod Sharma	P-11275.00	9695

27581 7590 09/12/2006

MEDTRONIC, INC.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/626,159	SHARMA, VINOD	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *8-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/4/05;3/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application was transferred to Examiner Quang Nguyen, Ph.D., in GAU 1633.

Claims 1-45 are pending in the present application.

Applicant's election with traverse of Group I (claims 1-7) in the reply filed on 8/7/06 is acknowledged. The traversal is on the ground(s) that there is no undue burden imposed on the Examiner to examine the subject application as originally filed. This is not found persuasive because the search for the Invention of Group I would not necessarily reveal all of the art relevant to other distinct inventions in other Groups. For example, the search for the bio-ablation composition of Group I would not encompass a composition containing a bio-pacemaker composition and/or an implantable pacemaker as required in other Groups. Moreover, it would be unduly burdensome for the examiner **to search and/or consider the patentability (examination) of all the inventions** in a single application (see MPEP § 803).

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 8-45 are withdrawn because they are directed to non-elected inventions.

Therefore, claims 1-7 are examined on the merits herein.

Specification

The disclosure is objected to because of the following informality: on page 15 in paragraph [0052], the co-pending U.S. Patent application serial number was not identified.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. 101 because the claims encompass a non-statutory subject matter.

Claims 1-7 are drawn to a bio-ablation composition comprising a coding sequence that encodes and expresses in atrioventricular node cells, a molecule that suppresses cellular excitability **and** a coding sequence that encodes and expresses a protein that decreases the conductance of an ion channel responsible for cellular excitability. The claims, as written, do not sufficiently distinguish over naturally occurring coding sequences for a molecule that suppresses cellular excitability and a protein that decreases the conductance of an ion channel responsible for cellular excitability because the claims do not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193

(1980). The claim should be amended to indicate the hand of the inventor. See MPEP 2105.

Additionally, since the bio-ablation composition is present or intended to be present in a human patient (particularly a human patient having a cardiac dysfunction), said composition becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of these claims, therefore, encompasses a human being, which is a non-statutory subject matter. See 1077 O.G. 24, April 21, 1987.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a bio-ablation composition comprising a coding sequence that **encodes and expresses in atrioventricular node cells, any molecule** that suppresses cellular excitability **and** a coding sequence that encodes and expresses **any protein** that decreases the conductance of an ion channel responsible for cellular excitability.

However, apart from the specific disclosure of using an exogenous polynucleotide encoding Kir/GEM (GenBank accession number U13052) to decrease levels of L-type Ca channels in atrioventicular node cells and thereby decrease the cell excitability (paragraph 0034); an exogenous polynucleotide encoding Giα subunit (GenBank accession number AH001470) to increase the dephosphorylation of the L-type Ca channel and thereby decreasing its conductance (paragraphs 0035-0036); and that the expression of L-type Ca channel can be suppressed through the use of the dominant negative Ca(v)1.2 with an ascidian 3-domain type alpha 1 subunit (paragraphs 0037 and 0072), the instant specification fails to describe relevant characteristics of a representative number of other species for **a broad genus** of a coding sequence that encodes and expresses in atrioventricular node cells a molecule that suppresses cellular excitability and a representative number of other species for **a broad genus** of a coding sequence that encodes and expresses a protein that decreases the conductance of an ion channel responsible for cellular excitability in the bio-ablation composition as claimed.

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure for a representative number of species for **a broad genus** of a coding sequence that encodes and expresses in atrioventricular node cells a molecule that suppresses cellular excitability and a representative number of species for **a broad genus** of a coding sequence that encodes and expresses a protein that decreases the conductance of an ion channel responsible for cellular excitability in the bio-ablation composition as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

When read in light of the specification, the sole purpose for the bio-ablation composition comprising a coding sequence that encodes and expresses in atrioventricular node cells, a molecule that suppresses cellular excitability and a coding sequence that encodes and expresses a protein that decreases the conductance of an ion channel responsible for cellular excitability is to attain a therapeutic effect in a subject in need thereof, particularly in a patient having a cardiac dysfunction such as arrhythmias (see at least paragraphs [0001], [0009]-[0010], [0012] and the title of the application). There is no other disclosed use for the bio-ablation composition as claimed. Since enablement requires the specification to teach how to make and **use** the claimed invention, the instant specification is not enabled for the presently claimed invention for the following reasons.

1. The breadth of the claims

The claims are directed to a bio-ablation composition comprising a coding sequence that encodes and expresses in atrioventricular node cells, **any molecule** that suppresses cellular excitability **and** a coding sequence that encodes and expresses **any protein** that decreases the conductance of **any ion channel** responsible for cellular excitability.

2. The state and the unpredictability of the art

At about the filing date of the present application (7/24/03), the attainment of any therapeutic effect via gene therapy, including gene therapy for the treatment of heart diseases such as cardiac arrhythmias, was and continues to be unpredictable as evidenced at least by the teachings of Tomaselli et al. (J. Cardiovascular Electrophysiology 14:547-550, 2003), Verma et al. (Annu. Revi. Biochem. 74:711-738, 2005), Goncalves (BioEssays 27:506-517, 2005) and Gardlik et al. (Med. Sci. Monit. 11:RA110-121, 2005). Tomaselli et al state that "The use of gene transfer in clinical therapeutics remains intellectually appealing but is subject to a number of substantial challenges before implementation in humans can be considered. These challenges are relevant to gene therapy generically and to the treatment of cardiac arrhymias specifically.", and "Problems that are more specific to gene therapy for cardiac arrthymias are exemplified by, but not limited to, our lack of understanding the molecular mechanisms of many arrhymias and the spatial complexity of expression of ion channels, which curbs the utility of transfer of a single ion channel species....Focal approaches to the delivery of genes or cells must confront the problems of accurate site selection and efficient and durable transduction of cells and/or the integration of

exogenous cells into the cardiac syncytium. The potential rewards of gene/cell therapy for cardiac arrhythmias are great; however, substantial challenges remain prior to implementation of such therapy in humans." (page 549, col. 2, second and fourth paragraphs). Even in 2005, Verma et al. still state "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but **it has yet to deliver its promised potential**", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, **gene therapy will be added to our medicinal armada** and the ever-expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph). Goncalves also states "Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph). Gardlik et al. (Med. Sci. Monit. 11:RA110-121, 2005) conclude "Although clinical trials have already started, **there are still numerous limitations that must be solved before routine clinical use**. Nevertheless, it can be expected that **future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last**" (page RA119, right-hand column, last paragraph).

3. The amount of direction or guidance presented

The instant specification fails to provide any evidence indicating that any therapeutic and/or prophylactic effect has been attained by the bio-ablation composition as claimed. Additionally, with respect to the breadth of the claims apart from the specific disclosure of using an exogenous polynucleotide encoding Kir/GEM (GenBank accession number U13052) to decrease levels of L-type Ca channels in atrioventicular node cells and thereby decrease the cell excitability (paragraph 0034); an exogenous polynucleotide encoding Giα subunit (GenBank accession number AH001470) to increase the dephosphorylation of the L-type Ca channel and thereby decreasing its conductance (paragraphs 0035-0036); and that the expression of L-type Ca channel can be suppressed through the use of the dominant negative Ca(v)1.2 with an ascidian 3-domain type alpha 1 subunit (paragraphs 0037 and 0072), the instant specification fails to sufficient guidance for a skilled artisan on how to use coding sequences encoding any other molecules that suppress cellular excitability or decrease the conductance of any ion channels responsible for cellular excitability in atrioventricular node cells, let alone for attaining the desired therapeutic effects contemplated by Applicants. In light of the state and the unpredictability of the prior art discussed above, coupled with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan on how to make and use the bio-ablation composition as claimed.

4. The amount of experimentation provided

The instant specification fails to provide any relevant example indicating that any therapeutic and/or prophylactic effect has been attained by the bio-ablation composition as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues raised above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the instant claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 and 6-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Donahue et al. (US 2002/0155101; IDS).

With respect to a composition claim, please note that its intended use is not given any patentable weight in light of the prior art. Additionally, as written the claims encompass a coding sequence that encodes a molecule that suppresses cellular excitability and a coding sequence that encodes and expresses a protein that decreases the conductance of an ion channel responsible for cellular excitability to be

the same coding sequence. By decreasing the conductance of an ion channel responsible for cellular excitability is one way to suppress the cellular excitability. Accordingly, the following rejection is applied.

Donahue et al. disclosed a composition comprising one or a combination of polynucleotides that encode the inhibitory Gαi2 subunit, G-protein subunit, connexin, gap junction protein and at least one ion channel protein including Ca channel subunits having dominant negative activity, and others (see at least the abstract; paragraphs 44-53). Donahue et al further disclosed that over-expression of Gαi2 subunit is capable of decreasing speed of conductance through the atrioventricular node in an animal system as determined by standard electrophysiological assay (paragraphs 0101-0104, and examples).

Since the composition taught by Donahue et al has the same component as a bio-ablation composition as broadly claimed, the reference anticipates the instant claims.

Please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, or are produced by identical **or** substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430,

433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donahue et al. (US 2002/0155101; IDS) in view of Murata et al. (Circulation 106:19, abstract 36, 2002; IDS).

Once again, please note that with respect to a composition claim, its intended use is not given any patentable weight in light of the prior art. Donahue et al. disclosed a composition comprising one or a combination of polynucleotides that encode the inhibitory Gαi2 subunit, G-protein subunit, connexin, gap junction protein and at least one ion channel protein including Ca channel subunits having dominant negative activity, and others (see at least the abstract; paragraphs 44-53). Donahue et al further disclosed that over-expression of Gαi2 subunit is capable of decreasing speed of conductance through the atrioventricular node in an animal as determined by standard electrophysiological assay (paragraphs 0101-0104, and examples).

Donahue et al does not teach specifically a composition further comprising a coding sequence of kir/GEM.

At the effective filing date of the present application, Murata et al already disclosed a vector encoding kir/GEM and that exogenous expression of kir/GEM reduced L-type calcium current that mimics pharmacological calcium channel blockade in adult guinea pigs (see the abstract). Murata et al further disclosed that kir/GEM was previously demonstrated reduce calcium current by inhibiting alpha subunit trafficking of L-type calcium channels in PC12 cells (decreasing expression of L-type calcium channels).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Donahue et al. by also incorporating a vector encoding kir/GEM in their composition to modulate the electrical property of the heart in an experimental model in light of the teachings of Murata et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Murata et al already disclosed that exogenous expression of kir/GEM reduced L-type calcium current that mimics pharmacological calcium channel blockade in adult guinea pigs.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Donahue et al., and Murata et al. The modified composition resulting from the combined teachings of Donahue et al. and Murata et al. is indistinguishable from the bio-ablation composition of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D
PATENT EXAMINER